

Neuroanatomical Profiles of Alexithymia Dimensions and Subtypes

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Abstract: Alexithymia, a major risk factor for a range of psychiatric and neurological disorders, has been recognized to comprise two dimensions, a cognitive dimension (difficulties identifying, analyzing, and verbalizing feelings) and an affective one (difficulties emotionalizing and fantasizing). Based on these dimensions, the existence of four distinct alexithymia subtypes has been proposed, but never empirically tested. In this study, 125 participants were assigned to four groups corresponding to the proposed alexithymia subtypes: Type I (impairment on both dimensions), Type II (impairment on the cognitive, but not the affective dimension), Type III (impairment on the affective, but not the cognitive dimension), and Lexithymics (no impairment on either dimension). By means of voxel-based morphometry, associations of the alexithymia dimensions and subtypes with gray and white matter volumes were analyzed. Type I and Type II alexithymia were characterized by gray matter volume reductions in the left amygdala and the thalamus. The cognitive dimension was further linked to volume reductions in the right amygdala, left posterior insula, precuneus, caudate, hippocampus, and parahippocampus. Type III alexithymia was marked by volume reduction in the MCC only, and the affective dimension was further characterized by larger sgACC volume. Moreover, individuals with the intermediate alexithymia Types II and III showed gray matter volume reductions in distinct regions, and had larger corpus callosum volumes compared to Lexithymics. These results substantiate the notion of a differential impact of the cognitive and affective alexithymia dimensions on brain morphology and provide evidence for separable neuroanatomical representations of the different alexithymia subtypes. *Hum Brain Mapp* 36:3805–3818, 2015. © 2015 Wiley Periodicals, Inc.

Key words: affective; cognitive; dimensions; corpus callosum; voxel-based morphometry

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INTRODUCTION

Alexithymia (no words for feelings) is a dimensional psychological construct that describes individuals who have difficulty identifying feelings, distinguishing them from physiological sensations of arousal, and describing their feelings to others. Moreover, alexithymic individuals lack imaginative abilities and exhibit an externally oriented cognitive style devoid of introspection [Sifneos, 1973; Vorst and Bermond, 2001]. With a prevalence rate of ten percent in the general population [Salminen et al., 1999], alexithymia constitutes a risk factor for a variety of psychiatric and neurological conditions [Taylor et al., 1999].

Growing evidence suggests that alexithymia is not a uniform construct but instead comprises two separable dimensions. Its cognitive dimension comprises difficulty identifying, analyzing, and verbalizing feelings and thus refers to deficient emotion processing at a cognitive level. In contrast, its affective dimension refers to the extent to which emotions are subjectively experienced and comprises difficulty emotionalizing (the extent to which an individual is emotionally aroused by emotion-inducing experiences) and fantasizing (the extent to which an individual is inclined to imagine, daydream etc.). In light of the heterogeneous nature of neurobiological findings characterizing four decades of alexithymia research and based on the two dimensions, Bermond hypothesized there may be subtypes of alexithymia, whose neural bases may differ and that may be differentially associated with psychopathology [Bermond et al., 2007]. Type I refers to the prototypical “cold-blooded” alexithymic individual that is characterized by low emotionality and poorly developed cognitions accompanying emotions, that is, who is impaired at both the affective and the cognitive dimension. This Type has been suggested to be a risk factor for psychopathy and schizoid personality disorder [Moormann et al., 2008]. Individuals with Type II alexithymia have a normal or even heightened emotionality but poorly developed cognitions accompanying the emotions, that is, they are selectively impaired at the cognitive dimension. This Type is considered to be a risk factor for borderline personality disorder and schizophrenia [Moormann et al., 2008; van der Meer et al., 2009]. Besides these two main types of alexithymia, a Type III has been proposed, whose cognitions accompanying the emotions are well developed but whose level of emotional experience is low, that is, such individuals are impaired at the affective but not the cognitive dimension. Lastly, the opposite of Type I “full-blown” alexithymia are “Lexithymics,” who have no impairment at either alexithymia dimension.

Although there is growing evidence for a differential association of the cognitive and affective alexithymia dimensions with function and structure of brain regions subserving emotion processing [Bermond et al., 2010; Goerlich-Dobre et al., 2014a; Goerlich et al., 2012; Pouga et al., 2010; van der Velde et al., 2014], Bermond’s differentiation between subtypes of alexithymia has hitherto been

purely theoretical. The aim of the present study was thus to put the alexithymia subtype distinction to a first test by analyzing evidence for differential neurobiological bases of different alexithymia subtypes.

Alexithymia has been proposed to result from (1) a deficit in interhemispheric transfer [Gazzaniga and LeDoux, 1978], (2) a right hemisphere dysfunction, or (3) dysfunction of the frontal cortex (for a review, see [Larsen et al., 2003]. Regarding specific brain regions, hypothesis (1) implicates the corpus callosum, which subserves interhemispheric communication necessary for cognitive emotion processing, in the cognitive alexithymia dimension and therefore in subtypes I and II. The anterior cingulate cortex (ACC), especially its dorsal portion (for a meta-analysis, see [van der Velde et al., 2013]) has been proposed to be a key region of alexithymia and may relate to both its cognitive and affective dimensions, given its relevance for emotional awareness [Lane et al., 1997; Wingbermühle et al., 2012] and its involvement in emotional experience [Milad et al., 2007] as well as in emotional tasks that are cognitively demanding [Phan et al., 2002]. Besides the ACC, the orbitofrontal cortex (OFC), amygdalae, and insulae have been linked to alexithymia, regions that are implicated in the early identification of emotion and the generation of emotional states [Adolphs et al., 2002; Phillips et al., 2003; Vuilleumier, 2005], and thus could be relevant to both alexithymia dimensions and thereby to all alexithymia subtypes. However, Bermond hypothesized medial OFC dysfunction to be specifically related to the affective alexithymia dimension [Bermond et al., 2006] and thus to the alexithymia subtypes I and III. Regarding the amygdalae, patients with unilateral or bilateral lesions to the amygdalae were able to report emotional feelings of normal intensity without any difference to healthy controls [Anderson and Phelps, 2002], which speaks against an involvement of the amygdalae in affective aspects of alexithymia [Wingbermühle et al., 2012] and suggests their involvement in the cognitive alexithymia dimension and thus in subtypes I and II. In addition to these regions, a recent meta-analysis demonstrated a robust involvement of the precuneus in alexithymia [van der Velde et al., 2013], a region implicated in higher-order cognitive functions related to insight and self-processing and mediating the integration of emotion, imagery, and memory [Fletcher et al., 1995; Maddock, 1999]; for a review see [Cavanna and Trimble, 2006], which should thus be associated with the cognitive alexithymia dimension and therefore with subtypes I and II.

Although the abovementioned regions have indeed been found to differ in volume as a function of alexithymia, the results of structural imaging studies are highly heterogeneous and inconsistent. Reduced white matter volume [Habib and Joly-Pottuz, 2003] and integrity [Kubota et al., 2012] of the corpus callosum were reported in alexithymic patients with multiple sclerosis and schizophrenia, respectively, whereas no corpus callosum differences were found

in a healthy control group in relation to alexithymia [Kubota et al., 2012]. Using surface area measurements, the ACC was found to be larger in surface in individuals scoring high on alexithymia [Gundel et al., 2004], whereas other studies using automated voxel-based morphometry (VBM) observed smaller gray matter volumes of the ACC [Borsci et al., 2009; Grabe et al., 2014; Ihme et al., 2013; Koven et al., 2011; Paradiso et al., 2008; Sturm and Levenson, 2011], or no association between alexithymia and ACC volume [Heinzel et al., 2012]. Similarly, previous studies reported either smaller [Borsci et al., 2009; Grabe et al., 2014; Ihme et al., 2013] or larger [Zhang et al., 2011] volumes of the insula, whereas others did not observe alexithymia-related differences in this structure [Heinzel et al., 2012; Kubota et al., 2011; Sturm and Levenson, 2011]. Smaller amygdala volume was observed in two studies [Grabe et al., 2014; Ihme et al., 2013], while others failed to find differences in amygdala volume [Borsci et al., 2009; Heinzel et al., 2012; Kubota et al., 2011].

The inconsistencies between previous findings could in part be due to the fact that all of the abovementioned studies used the Toronto Alexithymia Scale [TAS-20; Bagby et al., 1994] for alexithymia assessment, which takes into account only the cognitive alexithymia dimension but does not assess its affective dimension. For this reason, we recently performed two VBM studies differentiating between the two alexithymia dimensions. The results of these studies indicated that the cognitive dimension was related to larger right posterior insula volume [Goerlich-Dobre et al., 2014a] and smaller dorsal ACC volume [van der Velde et al., 2014], whereas the affective dimension was associated with larger middle cingulate cortex (MCC) volume [Goerlich-Dobre et al., 2014a], smaller OFC volume and reduced white matter volume in the right superior longitudinal fasciculus [van der Velde et al., 2014]. While the regions associated with the two alexithymia dimensions differed between the two studies, possibly due to different methodological approaches, these results do suggest that alexithymia comprises two separable dimensions that are linked to distinct morphological profiles.

The present VBM study aimed to take this research one step further by investigating not only the two alexithymia dimensions but also the proposed four subtypes of alexithymia. To this end, we subdivided a sample of 125 participants into four groups corresponding to the proposed alexithymia subtypes and employed a region of interest (ROI) approach to test whether the alexithymia dimensions and subtypes are differentially linked to variations in gray matter volume of regions previously associated with alexithymia: the ACC, MCC, OFC, precuneus, amygdalae, and insulae. Given functional and cytoarchitectonic differences between subregions of the ACC [Beckmann et al., 2009; Palomero-Gallagher et al., 2009; Vogt, 2005] and insula [Kurth et al., 2010] and our previous findings of associations of the alexithymia dimensions with subregions of the ACC [van der Velde et al., 2014] and insula [Goerlich-

Dobre et al., 2014a], the subgenual, pregenual, and dorsal ACC as well as the left and right anterior and posterior insula were included as ROIs. Furthermore, following the hypothesis of a deficit in interhemispheric transfer via the corpus callosum, this structure was included as an additional ROI. Based on our previous findings of structural differences between the cognitive and affective alexithymia dimensions, we hypothesized that the two dimensions would be associated with different patterns of volumetric alterations in these ROIs, with the cognitive dimension being related to ACC, amygdala, insula, and precuneus gray matter and corpus callosum white matter volume, and the affective dimension being related to MCC and OFC gray matter volume. Moreover, if there are indeed separable subtypes of alexithymia these might be linked to discernible structural correlates.

METHODS

Participants

Structural T1-weighted images of 125 (55 male) healthy subjects aged between 18 and 42 years were selected from a coauthor's previous neuroimaging study [Votinov et al., 2014] and one ongoing neuroimaging study at the University of Vienna.¹ All participants were right-handed as determined by the Edinburgh Handedness Inventory. Participants were native speakers of German with normal or corrected-to-normal vision, no hearing problems, and no psychiatric or neurological disorders in present or past according to self-report. Each participant gave informed consent prior to the respective study they participated in and received compensation for participation. The studies were approved by the ethics committee of the Medical University of Vienna and conducted in accordance with the Declaration of Helsinki.

Alexithymia Questionnaire

Before MR scanning, participants filled in the Bermond-Vorst Alexithymia Questionnaire [BVAQ; Vorst and Bermond, 2001]. The BVAQ is a 40-item self-report scale that comprises five subscales with eight items each: Identifying, verbalizing, analyzing, emotionalizing and fantasizing defined by Nemiah and Sifneos [Nemiah and Sifneos, 1970]. Answers are rated on a five-point Likert scale; higher scores indicate more pronounced alexithymic characteristics. Previous studies have confirmed the five-factor structure of the BVAQ and its good psychometric properties [Berthoz et al., 1999; Vorst and Bermond, 2001]. In contrast to the Toronto Alexithymia Scale (TAS-20), which assesses only the cognitive alexithymia dimension, the BVAQ makes it possible to assess both its affective and

¹Using TMS to treat smoking addiction: behavioral and neural effects.

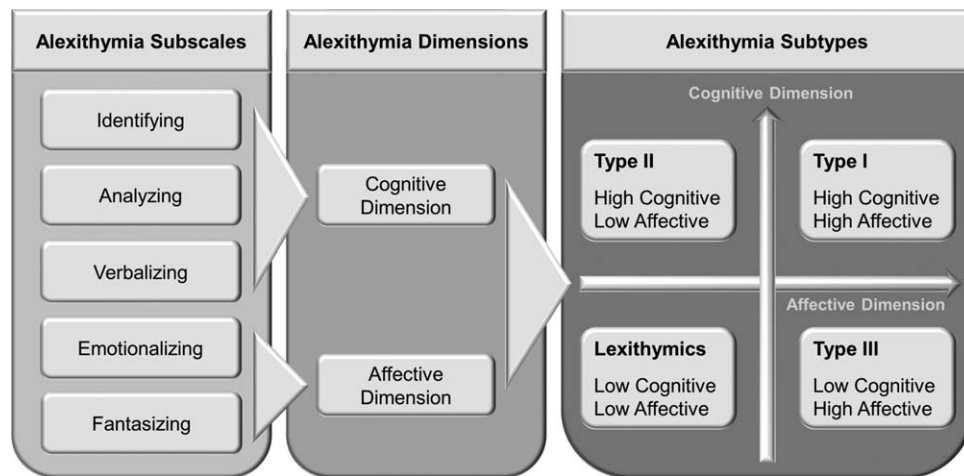


Figure 1.

Schematic overview of the four alexithymia subtypes, based on the cognitive and affective dimensions of alexithymia.

cognitive dimension by means of a second order factor structure that groups the factors difficulty identifying, verbalizing, and analyzing into the cognitive dimension, and the factors difficulty emotionalizing and fantasizing into the affective dimension of alexithymia. The validity of this two-factor structure has been confirmed through factor analyses by some [Bailey and Henry, 2007; Bekker et al., 2007; Bermond et al., 2007] but not all studies [Bagby et al., 2009]. The correlation between the cognitive dimension of the BVAQ and the total score of the TAS-20 is high ($r = 0.80$), indicating that they target the same alexithymic features [Vorst and Bermond, 2001].

Based on median splits of scores on the cognitive and the affective alexithymia dimensions, four groups were created in the present study that correspond to the proposed alexithymia subtypes (see Fig. 1): (1) Type I (high cognitive, high affective; $n = 30$), (2) Type II (high cognitive, low affective; $n = 32$), (3) Type III (low cognitive, high affective; $n = 22$), and (4) Lexithymics (low cognitive, low affective; $n = 34$), resulting in a total of 118 (51 male) participants. The remaining seven participants were excluded because their cognitive or affective score equaled the respective median.

MR Procedure

MR scanning was conducted on a 3 Tesla TIM Trio whole body scanner (Siemens, Germany) at the MR Center of Excellence, Medical University of Vienna, using a 32-channel head coil. For anatomical registration, high-resolution 3D T1 anatomical images were obtained (magnetization prepared rapid gradient echo sequence, 1 mm^3 isotropic voxels, repetition time (TR) = 2.3 s, echo time (TE) = 4.21 ms, 1.1 mm slice thickness, 900 ms inversion time, 9° flip angle).

Preprocessing

Imaging data were preprocessed using the VBM8 toolbox [Gaser, 2009] in SPM8 (Wellcome Department of Imaging Neuroscience Group, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) running under MATLAB 2012b (The MathWorks, Natick, MA). The images were reoriented to the intercommissural plane, corrected for field intensity inhomogeneities, and spatially normalized into standard space using the DARTEL default template of VBM8 within the same generative model [Ashburner and Friston, 2000]. Then, the images were segmented into gray matter, white matter, and cerebrospinal fluid, and modulated with Jacobian determinants. In modulated images, the total volume of gray matter equals that of the original images as modulation scales by the same amount of expansion or contraction applied during the preceding normalization. The modulated gray matter volumes were then smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM). This smoothing kernel is optimal for detecting morphometric differences in small as well as larger neural structures [Honea et al., 2005; White et al., 2001]. A homogeneity check identified no outliers, thus the normalized, modulated, and smoothed gray matter segments of all 118 participants were included in the subsequent statistical analyses.

VBM Analyses

VBM ROI gray matter analyses were performed on 13 a priori defined regions visualized in Figure 2: gray matter volumes of the MCC, OFC (medial), precuneus, amygdalae (left and right), anterior and posterior insulae (left and right), subgenual, pregenual, and dorsal ACC, and white matter volume of the corpus callosum. Anatomical ROIs for these regions were created using the automatic anatomic labeling (AAL) atlas templates [Tzourio-Mazoyer

Regions of Interest

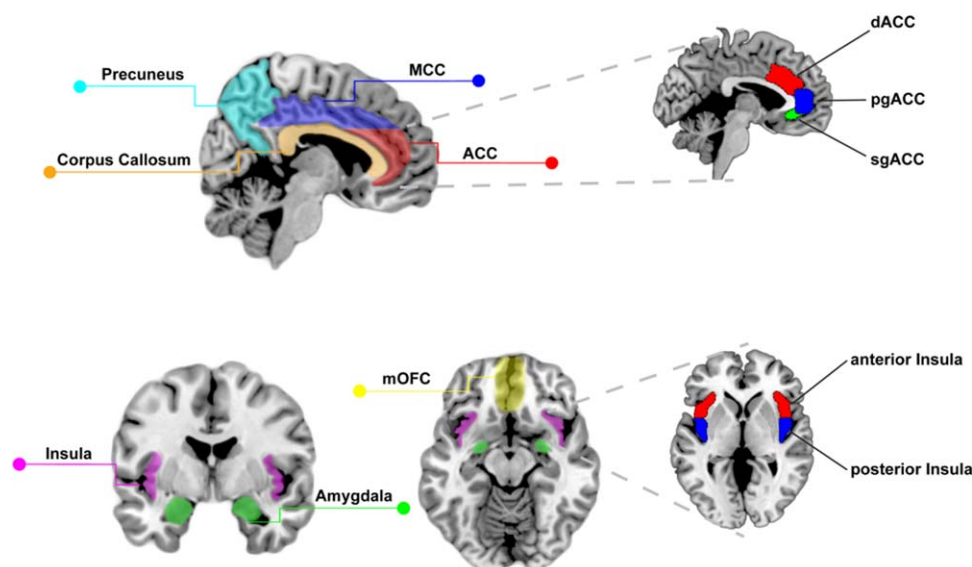


Figure 2.

A priori regions of interest (ROIs) included in the gray and white matter ROI analysis.

et al., 2002] provided by the WFU Pickatlas toolbox (Wake Forest School of Medicine, Winston Salem). Masks for the ACC and insula subregions were created using a modified version of the AAL atlas that contains a higher level of parcellation for the cingulate and insular cortex [Lord et al., 2012]. Mean parameter estimates of each ROI were then extracted using MarsBaR (<http://marsbar.sourceforge.net/>) for analysis in SPSS 20 (SPSS, Chicago, IL).

Two ROI analyses were performed: (1) associations of the alexithymia dimensions with ROI volumes were analyzed in a multivariate analysis of covariance (MANCOVA) with ROI as a within-subjects factor, the cognitive alexithymia dimension (high [Type I + II] vs. low [Type III + Lexithymics]) and the affective alexithymia dimension (high [Type I + III] vs. low [Type II + Lexithymics]) as between-subjects factors and (2) associations of the four alexithymia subtypes with ROI volumes were analyzed in a MANCOVA with ROI as a within-subjects factor and group (Type I, Type II, Type III, Lexithymics) as a between-subjects factor. Both analyses controlled for age and gender. MANCOVAs were chosen because these analyses take the nonindependence between the levels of the factor ROI into account. Significant effects were followed up by means of univariate analyses of covariance (ANCOVAs). Bonferroni correction was used to control for multiple comparisons. Effect sizes are reported using partial η^2 .

In addition, two whole-brain analyses were performed testing for (1) differences in gray matter volume between high- and low-scorers on the cognitive and the affective alexithymia dimension (two-sample *t*-tests), and for (2) dif-

ferences in gray matter volume between the four subtypes of alexithymia (2×2 full factorial design with two factors [cognitive, affective] with two levels each [high, low]). In both analyses, age and gender were included as covariates of no interest. Total intracranial volume (TIV) was not used as a covariate as the nonlinear images represent volume of gray matter that is already corrected for individual brain sizes. Results were considered significant if they survived FWE correction for multiple comparisons with the cluster-level threshold $p_{\text{FWE-corr.}} < 0.05$ and an initial voxel threshold $P < 0.001$. Coordinates of significant local maxima are reported in standard stereotaxic reference space (Montreal Neurological Institute, MNI).

RESULTS

One-way ANOVA revealed that the four groups corresponding to the alexithymia subtypes did not differ in gender [$F(3,114) = 0.28$, $P = 0.84$] and TIV [$F(3,114) = 0.35$, $P = 0.79$]. There was a significant difference in age [$F(3,114) = 5.38$, $P < 0.01$], confirming previous observations of increasing levels of alexithymia with age (e.g., [Pasini et al., 1992]. Table I shows the means, standard deviations, and range of scores on the cognitive and affective alexithymia dimensions within the four groups.

Gray matter

ROI Analysis: Dimensions

Pillai's trace showed a significant effect of the alexithymia dimensions on ROI volumes in the MANCOVA,

TABLE I. Means, standard deviation (SD), and range (minimum–maximum) of scores on the cognitive and affective alexithymia dimensions for the four alexithymia subtypes

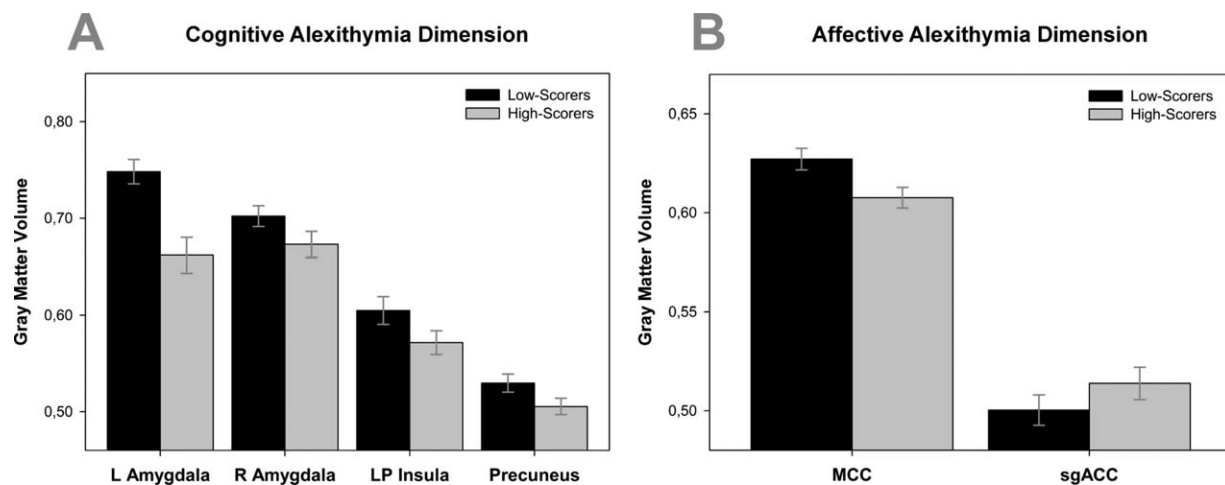
	Cognitive dimension			Affective dimension		
	Mean	SD	Range	Mean	SD	Range
Type I (high C, high A)	74.9	6.1	64–88	47.8	3.2	44–56
Type II (high C, low A)	73.9	7.4	64–98	37.4	3.7	28–42
Type III (low C, high A)	45.8	8.1	28–58	51.6	5.7	44–64
Lexithymics (low C, low A)	44.3	8.2	28–60	35.6	4.5	26–42

$V = 0.39$, $F(9,103) = 7.54$, $P < 0.001$. Univariate ANCOVAs for each ROI revealed that high scores on the cognitive alexithymia dimension were associated with reduced gray matter volume in the left amygdala [$F(1,111) = 42.03$, $P < 0.001$, $\text{partial } \eta^2 = 0.28$], the right amygdala [$F(1,111) = 5.63$, $P = 0.02$, $\text{partial } \eta^2 = 0.05$], the left posterior insula [$F(1,111) = 3.81$, $P = 0.02$, $\text{partial } \eta^2 = 0.05$], and the precuneus [$F(1,111) = 5.12$, $P = 0.03$, $\text{partial } \eta^2 = 0.04$]. In contrast, high scores on the affective alexithymia dimension were associated with reduced gray matter volume in the MCC [$F(1,111) = 4.73$, $P = 0.03$, $\text{partial } \eta^2 = 0.04$] and with increased gray matter volume in the subgenual ACC [$F(1,111) = 3.86$, $P = 0.05$, $\text{partial } \eta^2 = 0.03$]. There was no significant interaction between the cognitive and affective alexithymia dimensions on ROI gray matter volumes.

Figure 3 visualizes the differences in ROI gray matter volumes between low- and high-scorers on the cognitive and the affective alexithymia dimensions.

ROI Analysis: Subtypes

Pillai's trace showed a significant effect of the alexithymia subtypes on ROI volumes in the MANCOVA, $V = 0.66$, $F(39,306) = 2.22$, $P < 0.001$. Univariate ANCOVAs for each ROI revealed a significant main effect of group on gray matter volumes of the left amygdala [$F(3,112) = 13.94$, $P < 0.001$, $\text{partial } \eta^2 = 0.27$], resulting from significantly reduced left amygdala volume in individuals with Type I alexithymia (high cognitive, high affective; mean: 0.66) compared to Lexithymics (low cognitive, low affective; mean: 0.74; $P < 0.001$) and compared to individuals with Type III alexithymia (low cognitive, high affective; mean: 0.74; $P < 0.001$). In addition, a marginally significant main effect of group on volumes of the left posterior insula was observed [$F(3,112) = 2.43$, $P = 0.07$, $\text{partial } \eta^2 = 0.06$], resulting from significantly reduced left posterior insula volume in individuals with Type II (high cognitive, low affective; mean: 0.66) compared to Lexithymics (low cognitive, low affective; mean: 0.74; $P < 0.001$).

**Figure 3.**

Results of the ROI gray matter analysis. (A) Low- versus high-scorers on the cognitive alexithymia dimension. (B) Low- versus high-scorers on the affective alexithymia dimension. Significance threshold $P < 0.05$ Bonferroni-corrected. Error bars indicate 95% confidence intervals. L—left, R—right, LP—Left Posterior, MCC—middle cingulate cortex, sgACC—subgenual anterior cingulate cortex.

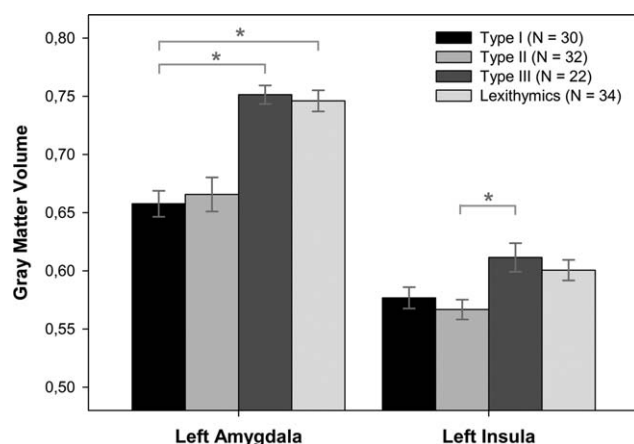


Figure 4.

Results of the ROI gray matter analysis for the four alexithymia subtypes. Significance threshold $P < 0.05$ Bonferroni-corrected. Error bars indicate 95% confidence intervals.

mean: 0.57) compared to those with Type III alexithymia (low cognitive, high affective; mean: 0.61; $P < 0.05$). Note that the effect of group on gray matter volumes of the right amygdala, precuneus, MCC and on white matter volumes of the corpus callosum just failed to reach significance (right amygdala, $P < 0.10$; precuneus, $P < 0.12$; MCC, $P < 0.15$; corpus callosum, $P < 0.15$).

Figure 4 visualizes the differences in gray matter volumes of the left amygdala and the left posterior insula between the alexithymia subtypes.

TABLE II. Whole-brain gray matter volume differences between high- and low-scorers on the cognitive and affective alexithymia dimensions, respectively, corrected for multiple comparisons at $p_{FWE-corr} < 0.05$ cluster level

	Brain area (aal)	Cluster size	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i> -score
Cognitive dimension						
Low > High	L Thalamus	12902	−15	−19	6	8.38
	L Thalamus		−16	−18	13	8.38
	L Amygdala		−27	−4	−22	8.08
	L Thalamus		−12	−19	0	7.53
	R Thalamus		16	−15	12	6.17
	L Thalamus		−9	−6	4	6.12
	R Thalamus		16	−16	7	6.09
	L Caudate		−7	−7	0	5.96
	R Thalamus		15	−19	0	5.76
	R Thalamus		12	−16	−1	5.43
	L Parahippocampal gyrus		−12	1	−24	5.38
	L Hippocampus		−13	−37	1	4.73
	L Thalamus		−1	−18	15	4.51
	L Insula		−40	12	−6	4.09
	R Thalamus		10	−6	4	3.64
High > Low	none					
Affective dimension						
Low > High	L Middle cingulum	156	−14	−11	42	4.81
	R Middle cingulum		18	−32	48	3.30
	L Middle cingulum		−8	−42	53	3.19
High > Low	none					

Whole-Brain Analysis: Dimensions

Table II lists the results of the whole-brain two-sample *t*-tests between high- and low-scorers on the cognitive and affective alexithymia dimensions, respectively. The contrast low- versus high-scorers on the cognitive dimension confirmed the volume reduction in the left amygdala and the left insula observed in the ROI analysis. In addition, the whole-brain analysis revealed that high-scorers on the cognitive dimension had also reduced gray matter volumes in the left and right thalamus, caudate, hippocampus, and parahippocampal gyrus (cluster size 12,576 voxels; peak coordinate $x = -17$, $y = -18$, $z = 14$). The reversed contrast (cognitive high- vs. low-scorers) yielded no significant results. The contrast low- versus high-scorers on the affective dimension confirmed the results of the ROI analysis by showing a volume reduction in the MCC in affective high-scorers (cluster size 158 voxels; peak coordinate $x = -12$, $y = -11$, $z = 42$). No other brain regions were found to differ in volume between high- and low-scorers on the affective dimension, and the reversed contrast (cognitive high- vs. low-scorers) yielded no significant results. Whole-brain gray matter volume differences in relation to the cognitive and affective alexithymia dimensions are visualized in Figure 5.

Whole-Brain Analysis: Subtypes

Table III lists the results of the full factorial design comparing the four alexithymia subtypes. Compared to Lexithymics (low cognitive, low affective), individuals with

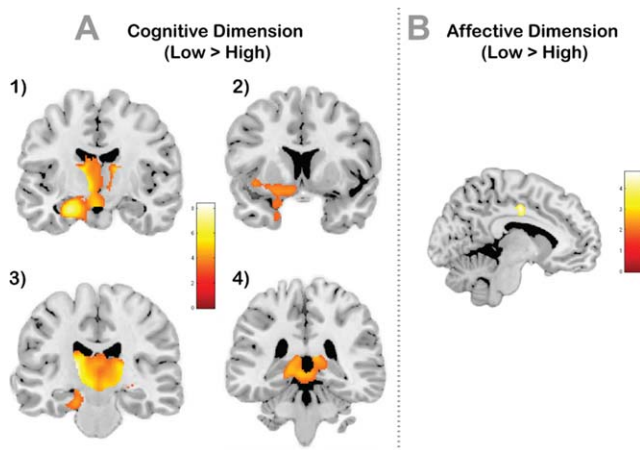


Figure 5.

Whole-brain gray matter volume differences between alexithymia dimensions. (A) Low- versus high-scorers on the cognitive alexithymia dimension. (1) amygdala, thalamus, (2) caudate, insula, (3) insula, thalamus, (4) hippocampus. (B) Low- versus high-scorers on the affective alexithymia dimension, MCC. Results are visualized at $P < 0.001$ uncorrected.

Type I alexithymia (high cognitive, high affective) had less gray matter volume in a large cluster (5801 voxels) in the left hemisphere, centered around the thalamus, hippocampus, and the amygdala (peak coordinate $x = -17$, $y = -7$, $z = -23$). A similar, albeit smaller cluster (2507 voxels) of reduced gray matter volume in the left thalamus and amygdala was observed in individuals with Type II alexithymia (high cognitive, low affective) compared to Lexi-

TABLE III. Whole-brain gray matter volume differences between the four subtypes of alexithymia, corrected for multiple comparisons at $p_{FWE-corr} < 0.05$ cluster level

Brain area (aal)	Cluster size	x	y	z	T -score
Lexithymics > Type I					
L Hippocampus	5801	-27	-7	-23	6.30
L Thalamus		-17	-18	13	6.04
L Amygdala		-23	-2	-24	5.65
Lexithymics > Type II					
L Thalamus	2507	-15	-19	6	5.75
L Amygdala		-26	-4	-23	5.49
L Thalamus		-11	-6	7	4.68
Lexithymics > Type III					
MCC	54	9	-37	51	3.79
MCC	64	17	-15	45	3.72
Type II > Type III					
MCC	106	-15	-9	42	4.11
Type III > Type II					
L Thalamus	6314	-15	-19	6	6.61
L Thalamus		-17	-18	13	5.65
L Amygdala		-27	-3	-23	5.64

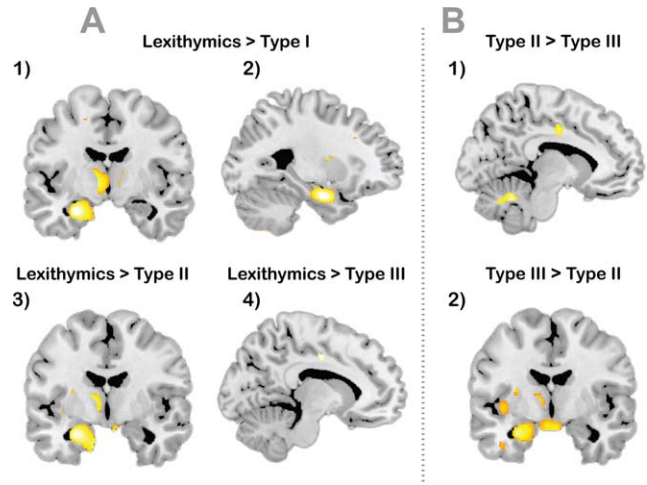


Figure 6.

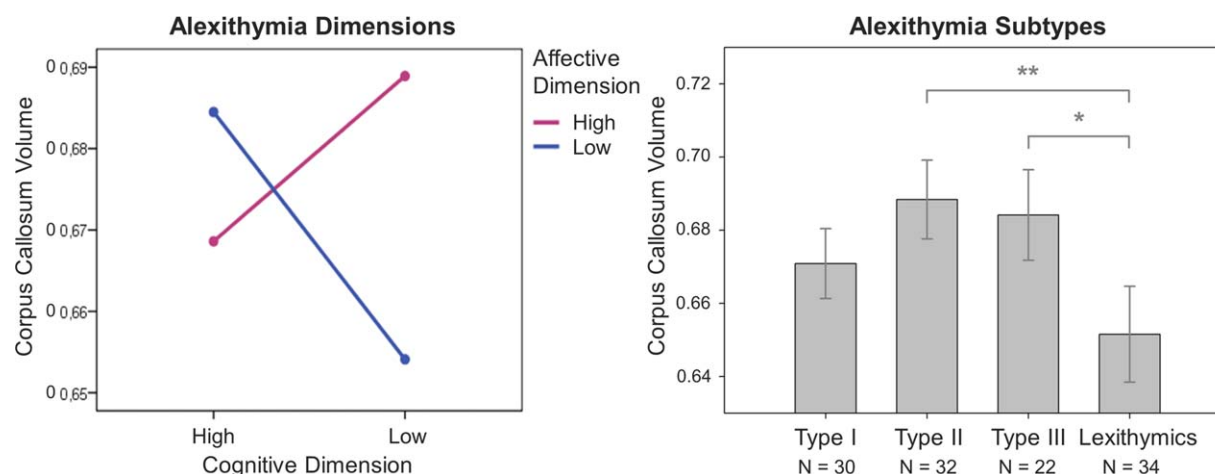
Whole-brain gray matter volume differences between the four alexithymia subtypes. (A) (1) and (2): Lexithymics > Type I, (3) Lexithymics > Type II, (4) Lexithymics > Type III. (B) (1) Type II > Type III, (2) Type III > Type II. Results are visualized at $P < 0.001$ uncorrected.

thymics (peak coordinate $x = -15$, $y = -19$, $z = 6$). As Type II alexithymia differs from Lexithymics only on the cognitive alexithymia dimension, this confirms the results of the dimensional analysis, showing that the cognitive alexithymia dimension is linked to gray matter volume reductions in the left amygdala and the thalamus.

In contrast, individuals with Type III alexithymia (low cognitive, high affective) had reduced gray matter volume in two clusters within the MCC compared to Lexithymics (after SVC; 54 and 64 voxels, respectively). This confirms the result of the dimensional analysis and shows that volume reductions in the MCC are specific to the affective alexithymia dimension.

Contrasting the intermediate subtypes, individuals with Type III alexithymia (low cognitive, high affective) had less gray matter volume in a small cluster within the MCC (106 voxels) compared to individuals with Type II alexithymia (high cognitive, low affective), whereas individuals with Type III alexithymia (low cognitive, high affective) compared to those with Type II alexithymia (high cognitive, low affective) had less gray matter volume in a large cluster (6314 voxels) centered around the left thalamus and the left amygdala, similar to the clusters identified for the contrasts Type I (high cognitive, high affective) versus Lexithymics and Type II (high cognitive, low affective) versus Lexithymics. Whole-brain gray matter volume differences in relation to the four subtypes of alexithymia are visualized in Figure 6.

Overall, the results of the gray matter volume analyses indicate that differences in brain morphology in relation to the affective alexithymia dimension are restricted to the

**Figure 7.**

Corpus callosum mean volume in relation to the alexithymia dimensions (left) and subtypes (right). Error bars indicate the standard error of the mean. ** $P < 0.05$, * $P < 0.06$.

cingulate cortex, whereas the cognitive dimension seems to be linked to structural differences that are more pronounced and comprise large volume reductions in a network of regions, including the amygdala, the precuneus, and the insula.

White Matter: Corpus Callosum

A significant interaction between the two alexithymia dimensions and white matter volume of the corpus callosum was observed [$F(1,111) = 5.05$, $P = 0.03$, *partial* $\eta^2 = 0.04$]. This interaction revealed that corpus callosum volume was significantly larger in individuals with Type II alexithymia compared to Lexithymics (Type II: 0.688 ± 0.061 vs. Lexithymics: 0.652 ± 0.077 ; $F(1,61) = 4.61$, $P = 0.04$), and tended to be larger in individuals with Type III alexithymia compared to Lexithymics (Type III: 0.684 ± 0.058 vs. Lexithymics: 0.652 ± 0.077 ; $F(1,51) = 2.86$, $P = 0.09$), whereas the difference between the two extreme groups, that is, Type I alexithymia (high scores on both dimensions) and Lexithymics (low scores on both dimensions) was not significant (Type I: 0.671 ± 0.052 vs. Lexithymics: 0.652 ± 0.077 ; $F(1,59) = 1.34$, $P = 0.25$). Figure 7 visualizes this interaction and the resulting reversed U-shape pattern characterizing the relationship between the alexithymia subtypes and corpus callosum volume.

DISCUSSION

This study investigated the structural correlates of the cognitive and affective alexithymia dimensions and aimed to find out whether there is morphological evidence for the hitherto theoretical concept of different alexithymia

subtypes. We found that Type I and Type II alexithymia (both marked by high scorers on the cognitive dimension) were characterized by gray matter volume reduction in the left amygdala and in addition in the thalamus, which was more pronounced in the extreme Type I than in the intermediate Type II. In addition, the cognitive dimension was linked to volume reductions in the right amygdala, the left posterior insula, and in the precuneus, caudate, hippocampus, and parahippocampus. In contrast, Type III alexithymia (marked by high scores on the affective dimension) was marked by volume reduction in the MCC only, and the affective dimension was further characterized by larger sgACC volume. Moreover, individuals with the intermediate Types II and III showed gray matter volume reductions in distinct regions, and had larger corpus callosum volumes compared to Lexithymics. These results substantiate recent findings of a differential impact of the cognitive and affective alexithymia dimensions on brain morphology and provide the first neuroanatomical evidence for the existence of separable alexithymia subtypes.

Despite extensive research into the neural basis of alexithymia, it is still unclear which neural correlates underlie the profound emotion processing difficulties characteristic of this personality construct. For instance, there is no consensus as to whether alexithymia primarily hampers early, automatic processes involved in the perception and recognition of emotions below the level of conscious awareness, or rather late processes guiding the conscious experience of emotions and their cognitive control and regulation. The present findings indicate a reduction of gray matter volume in the amygdalae and insula, structures that are involved in automatic emotion processing, in individuals scoring high on the cognitive alexithymia dimension (Type I and Type II alexithymia). This confirms functional

imaging findings indicating reduced activation of the amygdalae and insulae in alexithymia [for a meta-analysis, see van der Velde et al., 2013], and is in line with a recent report of aberrant neurotransmitter concentrations in the insula and the ACC in alexithymia [Ernst et al., 2014]. Kugel et al. reported a negative correlation between TAS-20 (i.e., cognitive) alexithymia scores and amygdala reactivity to masked emotional faces [Kugel et al., 2008], a finding that was replicated by Reker et al., who used the same paradigm and additionally observed reduced automatic activation of the insula [Reker et al., 2010]. Although not identified in all studies [e.g., Heinzel et al., 2012; van der Velde et al., 2014], both the amygdalae and the insulae have indeed been found to differ in volume as a function of alexithymia by previous VBM studies employing the TAS-20 scale (and thus assessing the cognitive alexithymia dimension): Ihme et al. reported reduced left amygdala ROI volume in 17 high- compared to 17 low-scorers on alexithymia [Ihme et al., 2013], a finding that was confirmed by a recently published large-scale study, which reported reduced gray matter volumes in the right amygdala and the left insula in 844 male participants [Grabe et al., 2014]. Moreover, several studies reported differences in insula volume in relation to high levels of alexithymia [Borsci et al., 2009; Goerlich-Dobre et al., 2014a; Ihme et al., 2013; Zhang et al., 2011]. The present results of reduced bilateral amygdalae and left posterior insula volume confirm these findings and suggest that gray matter volume differences in these regions are specific to the cognitive alexithymia dimension. Given the involvement of the amygdala and insula in automatic emotion processing, such volume alterations could underlie impairments in the early, automatic processing of emotions previously observed in alexithymia [Goerlich-Dobre et al., 2014b; Kugel et al., 2008; Reker et al., 2010].

Besides the amygdalae and the left insula, the present results show reduced gray matter volume in the precuneus in high-scorers compared to low-scorers on the cognitive alexithymia dimension. The precuneus plays a central role in visuo-spatial imagery, episodic memory retrieval, and self-processing operations such as attributing emotions to oneself and others [Ochsner et al., 2004; for a review see Cavanna and Trimble, 2006]. Its robust involvement in emotion processing difficulties in alexithymia has recently been demonstrated by a meta-analysis [van der Velde et al., 2013], which reported reduced precuneus activity in response to positive stimuli in individuals with high levels of alexithymia. Two previous VBM studies on alexithymia observed reduced gray matter volume in this region in high- compared to low-scorers on alexithymia [Borsci et al., 2009; Sturm and Levenson, 2011]. The present result of reduced precuneus volume in high- versus low-scorers on the cognitive alexithymia dimension corroborates these findings and indicates that volume reduction in this region may be attributed to difficulties in the cognitive processing of emotions rather than to a reduction in the subjective

experience of feelings. Moreover, a whole-brain analysis revealed that gray matter volume reductions associated with the cognitive alexithymia dimension were not restricted to the amygdalae, insula, and precuneus, but extended to other limbic and paralimbic regions including the thalamus, hippocampus, parahippocampal gyrus, and caudate, suggesting that volume reductions in a network of regions underlie deficits in emotion recognition, identification, and regulation characterizing the cognitive alexithymia dimension.

The affective alexithymia dimension was associated with larger subgenual ACC (sgACC) and reduced MCC volume in this study. Regarding the ACC, this is in line with previous studies reporting that alexithymia is associated with differences in ACC volume [e.g., Ihme et al., 2013; Paradiso et al., 2008; Sturm and Levenson, 2011], with reduced ACC functioning [e.g., Karlsson et al., 2008; Reker et al., 2010] and connectivity [Liemburg et al., 2012], and with increased gamma-aminobutyric acid (GABA) transmission mediating decreased neural activity in the ACC [Ernst et al., 2014]. Moreover, these results confirm our hypothesis of a specific involvement of the MCC in the affective alexithymia dimension. This finds further support in the present findings of reduced MCC volume in (a) Type III alexithymia compared to Lexithymics, who differ from each other only on the affective dimension, and (b) in Type III alexithymia, characterized by high scores on the affective dimension compared to individuals with Type II alexithymia, who have low affective scores. Interestingly, in a previous study we observed a positive correlation between affective alexithymia scores and MCC volume [Goerlich-Dobre et al., 2014a], whereas the present results show a negative relationship. However, the previous result was based only on the emotionalizing facet of the affective dimension, and the statistical power of the previous correlational analysis was insufficient due to the small sample size ($n = 32$), which is why we cautioned to consider this result as preliminary. Our present finding, based on a much larger sample size ($n = 118$), thus higher statistical power, and taking into account the complete affective dimension in fact suggests reduced MCC volume. Considering that the MCC seems to be preferentially involved in mentalizing and judgements about oneself compared to those about others [Lombardo et al., 2010], reduced MCC volume as found in the present study could underlie reduced emotional self-awareness, the core deficit of alexithymia [Lane et al., 1997].

Combining our findings regarding ACC volume differences observed in the present study and in our previous study [van der Velde et al., 2014], there seems to be a link between the affective alexithymia dimension and sgACC volume as well as MCC volume [Goerlich-Dobre et al., 2014a; present study], and between the cognitive alexithymia dimension and dorsal ACC (dACC) volume [van der Velde et al., 2014]. Thus, both dimensions may be associated with differences in gray matter volumes of the cingulate cortex, but

they appear to affect different subregions of this structure. Regarding the ACC subregions, our results of dACC volume being linked to the cognitive and sgACC volume to the affective alexithymia dimension are in line with the view of a dorsal-caudal “cognitive” and a ventral-rostral “affective” functional subdivision of the ACC [Bush et al., 2000], but may be more precisely interpreted in light of a recent refinement of this model [Etkin et al., 2011]. The latter states that the dACC, which shows strong connectivity with core emotion-processing areas such as the amygdalae [Amaral et al., 1992] is involved in the expression of negative emotion and cognitive reappraisal [see also Giuliani et al., 2011], whereas ventral-rostral portions of the ACC and medial prefrontal cortex have a regulatory role with respect to limbic regions involved in generating emotional responses. In experimental animals, the sgACC has been proposed to be part of an extended “visceromotor network,” which modulates autonomic/neuroendocrine responses and neurotransmitter transmission during the neural processing of reward, fear, and stress [Drevets et al., 2008]. Given these functional differences between subregions of the ACC, reduced dACC volume as found in individuals scoring high on the cognitive alexithymia dimension may underlie the difficulty of these individuals to cognitively regulate and verbalize particularly negative emotions, while enhanced sgACC volume in individuals scoring high on the affective alexithymia dimension may arise from an over-regulation of limbic regions by the sgACC, resulting in the lack of emotional experience characteristic of these individuals. However, this interpretation should be considered speculative and further studies are needed to elucidate the specific morphological underpinnings of the alexithymia dimensions, particularly with respect to subregions of the ACC.

The present results not only confirm our hypothesis of specific structural correlates underlying the cognitive and affective alexithymia dimensions, but show for the first time that the different subtypes of alexithymia are characterized by gray matter volume differences in distinct regions, and also by white matter volume differences: Individuals with Type II alexithymia had significantly larger corpus callosum volumes than Lexithymics, and individuals with Type III alexithymia tended to show the same effect. This suggests that high scores on either the affective (Type III) or the cognitive (Type II) alexithymia dimension are linked to larger compared callosum volume, compared to Lexithymics. Surprisingly, corpus callosum volumes in Type I alexithymia, that is, high scores on both dimensions, were not significantly larger than in Lexithymics in the present sample, resulting in a reversed U-shape pattern characterizing the relationship between the alexithymia subtypes and corpus callosum volume.

The corpus callosum, a white matter structure that comprises myelinated axons connecting the two hemispheres, has a long history in alexithymia research due to its central role in the interhemispheric transfer of emotion from the right hemisphere to the verbalizing left hemisphere

[Gazzaniga and LeDoux, 1978]. Split-brain patients who had undergone complete commissurotomy because of severe epilepsy were found to be highly alexithymic post-surgery. Specifically, they experienced problems expressing feelings verbally, and their ability to fantasize, symbolize, and dream had significantly decreased [Hoppe and Bogen, 1977]. This relationship between alexithymia and a deficit in interhemispheric communication was confirmed by several subsequent studies on split-brain patients [TenHouten et al., 1986], patients with corpus callosum agenesis [Buchanan et al., 1980; Ernst et al., 1999] and post-traumatic stress disorder [Zeitlin et al., 1989], and healthy participants [Dewaraja and Sasaki, 1990; Parker et al., 1999]. At first glance, our result of larger corpus callosum volume in Type II and Type III alexithymia compared to Lexithymics may seem to contradict the model of an interhemispheric transfer deficit in alexithymia [Hoppe and Bogen, 1977], which implies a lack of communication between the two hemispheres, which then gives rise to problems communicating emotions. However, transcranial magnetic stimulation (TMS) studies that directly tested the time required for information to travel from one hemisphere to the other (transcallosal transmission time) found that high scores on alexithymia were associated with shorter, rather than prolonged transmission times between the hemispheres [Grabe et al., 2014; Lang et al., 2011; Romei et al., 2008]. The present finding of increased corpus callosum volume in Type II and Type III alexithymia could underlie this faster transcallosal transmission, possibly through increased myelination of transcallosal axons resulting in overall larger corpus callosum volume. Note that *faster* transcallosal transmission does not necessarily imply *more efficient* interhemispheric communication and integration, because fast connections may induce noise due to unnecessary crosstalk between separate processing systems [Doron and Gazzaniga, 2008]. Indeed, the integrity of white matter tracts in the corpus callosum has been found significantly reduced as a function of alexithymia [Kubota et al., 2012]. Taken together, transcallosal connectivity appears to be disrupted in individuals with Type II and Type III alexithymia, resulting in less efficient information transfer despite (or possibly because) overall larger corpus callosum volume as identified in the present study. At this point, it is not clear whether the here observed enlargement in corpus callosum volume in the alexithymia Types II and III are qualitatively similar or the result of different underlying processes. Future research is needed to replicate the observed differences in corpus callosum volumes in larger samples, possibly revealing significant differences between Type I alexithymia and Lexithymics as well. Importantly, future studies should attempt elucidating the neurobiological mechanisms and aberrations in callosal microstructure that give rise to the observed differences in corpus callosum volume between the alexithymia subtypes. In a follow-up study, we plan to use diffusion tensor imaging

(DTI) tractography to gain insight into the strength and directions of fiber pathways coursing through the corpus callosum and of the pathways connecting the identified regions of interests, such as the amygdalae, insulae, and MCC, with other regions of the brain.

Moreover, a useful future direction would be investigating the level of functional connectivity between the identified regions during emotion processing and to identify the link between functional and structural differences associated with the alexithymia dimensions and subtypes. The identified regions could then be modulated using techniques such as TMS or transcranial direct current stimulation (tDCS) with the aim to enhance the level of emotional experience (affective dimension) and/or the level of cognitive emotion control (cognitive dimension). Further future directions could include more thorough investigations into neurotransmitter concentrations in the identified key regions, such as the recently reported increase of GABA concentration in the ACC [Ernst et al., 2014], with the aim to elucidate their specific associations with the different alexithymia dimensions and subtypes. Such research could eventually enable pharmacological manipulations targeting these regions in clinical samples.

To sum up, the results of the present study confirm the notion that the cognitive and affective alexithymia dimensions have dissociable morphological profiles, with the cognitive dimension being linked to pronounced gray matter volume differences in a network of limbic and paralimbic regions, including the amygdala, insula, and precuneus, and the affective dimension being associated with comparably smaller and focal gray matter volume alterations restricted to the cingulate cortex. Moreover, they provide first evidence for separable neuroanatomical representations of the different alexithymia subtypes with respect to both gray and white matter volumes. In this regard, it should be noted that the groups corresponding to the four proposed alexithymia subtypes were created based on median splits on the cognitive and affective alexithymia dimensions in the present study, although Bermond and colleagues suggested to include only individuals scoring lower than the 30th percentile and those scoring higher than the 70th percentile on the cognitive and affective dimension, respectively [Moormann et al., 2008]. The current sample size did not allow following those stricter criteria as this would have resulted in very small subgroup sizes (Type I: $n = 13$, Type II: $n = 9$, Type III: $n = 11$, Lexithymics: $n = 16$) with presumably insufficient statistical power. However, the fact that even with our more lenient criteria significant differences in gray and white matter volumes were observed indicates that the alexithymia subtypes are indeed associated with separable morphological profiles, which can be more reliably discerned using stricter selection criteria and larger sample sizes in further studies. In conclusion, the present findings create a promising prospect for future studies aiming to further disentangle the

neural substrates underlying the different alexithymia subtypes and their predictive power for specific types of psychopathology.

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